Remarks

Claims 38-42, 49, 81-90, 98 and 99 are currently under examination in this application. Applicant has amended claims 38, 49, 81 and 84. No new matter is added by virtue of the amendments contained herein. Support for the amendments lies in the claims and specification as filed. Applicants responds fully to each of Examiner's rejections as follows.

Information Disclosure Statement

The Examiner objected to the information disclosure statement filed 9/12/2005 as failing to comply with 37 CFR1.98(a)(3) because it did not include a complete concise explanation of the relevance of submitted EP1144623. Applicant provides herewith a copy of the front page of Canadian application equivalent of EP1144623, Canadian application 2359180, which contains an english abstract of the invention as an english summary of EP1144623. Additionally provided are the english translation of claims granted in EP1144623. Consideration of the EP1144623 submission is requested.

Indefiniteness

The Examiner rejected claims 38-42 and 49 under § 112, second paragraph as being indefinite, for being dependent on withdrawn claims 1 and 23. Claims 38 and 49 have been amended herewith to incorporate the limitations of withdrawn claims 1 and 23. It is believed the present amendments render the rejection moot. Withdrawal of the rejection is respectfully requested.

The Examiner rejected claims 38-42 under § 112, second paragraph as being indefinite. The Examiner alleges "it is not clear how introducing the composition into the vascular system of the subject is administering a composition to the respiratory system of a subject." Applicant respectfully traverses this rejection. Delivery of agents to the respiratory system via intravenous delivery has been accomplished. See, e.g., Griesenbach, U., et al.(IDS, submitted). Applicant respectfully submits that many respiratory diseases are treated by vascular delivery (e.g., by parenteral injection). It is well understood in the art that introduction of a pharmaceutical composition via vascular delivery may be a preferred route of administration for delivery of an agent to the respiratory system of a subject. This mode of treatment may be necessary, e.g., in patients having highly compromised respiratory function in which pulmonary delivery is not an option. Applicant further refers the Examiner to results discussed below in response to the enablement rejection, showing that influenza virus infection can be treated by intravenous (iv) delivery of siRNA.

However, in an effort to address the Examiner's concern, Applicant has amended claim 38 to recite "delivering" in lieu of "administering" a composition to the respiratory system. Applicant submits the amendment is not made with any concession that any clarification is required. For any or all of these reasons, applicant respectfully requests Examiner to withdraw this rejection.

Description

The Examiner rejected claims 38-42, 49, 81-90, 98 and 99 under § 112, first paragraph for lack of written description, for reciting "an RNAi inducing entity" and "a target transcript." Applicant respectfully traverses this rejection.

The standard for compliance with the written description requirement is "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed?" (emphasis added, MPEP 2163.02, citing *In re Gosteli* 10 USPQ2d 1614 (Fed. Cir. 1989). That is, whether, the written description relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter" (emphasis added, MPEP 2163.02, citing *Palston Purina v. Far Mar Co.* 227 USPQ 177 (Fed. Cir. 1985). The burden is on the Examiner is to "present evidence or reasons why persons skilled in the art would not recognize in applicant's disclosure a description of the invention defined by the claims" (MPEP 2163.04, citing *In re Wertheim* 191 USPQ 90 (CCPA 1976).

Applicant submits the Examiner's focus on limitations and/or specific recitations of RNAi inducing entity or a target transcript are undue. As discussed in the background of the invention, and in additional cited articles, mechanisms of RNAi, components used for initiation of RNAi as well as target transcripts and associated sequences useful for inhibition of target sequences were well known in the art and/or readily available at the time of Applicant's filing of the present application. However, a need existed for improved compositions and methods for delivery of RNAi-inducing entities in order to realize in vivo benefits of this technology. See, e.g. paragraph 005. Applicant submits the present invention provides such improved compositions and methods, which are applicable to a wide range of species of RNAi-inducing agents, target transcripts and associated sequences. Applicant points out the skill and knowledge in the art relating to RNAi-inducing entities, and target transcripts and associated sequences is high. Applicant further submits that when, as is the case for RNAi inducing entities and target transcripts and associated sequences, one skilled in the art would readily envision from the description and claims provided by the invention, the entire scope of the invention, and would readily envision the metes and bounds of the provided claimed subject matter, such claims are not to be found lacking for written description. Thus, simply because a range of modalities or entities may be useful in conjuction with a

method or composition as claimed does not render claims indefinite. "In general, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement. Information which is well known in the art need not be described in detail in the specification." See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986).

The Examiner has failed to satisfy the burden of proof by providing any evidence or reasons as to why Applicant's disclosure fails for sufficient description. The Examiner instead incorrectly requires Applicant to "provide a written description of the RNAi inducing entity that is required to practice the instantly claimed invention" (at p. 6, emphasis added). On the contrary, Examiner's own statements characterizing Applicant's invention as claimed evince that Applicant's description is in fact adequate to convey the scope of the invention as claimed to the Examiner, and hence to one of ordinary skill.

Without disclaimer, waiver or prejudice, and without withdrawing Applicant's reasons for traversing Examiner's instant rejection of the claims, Applicant amends claims 38,49, 81, and 84 to recite:

... an RNAi-inducing entity, wherein the RNAi-inducing entity is selected from an siRNA, and shRNA, or an RNAi-inducing vector whose presence within a cell results in production of an siRNA or shRNA; wherein the siRNA, shRNA, or the siRNA or shRNA produced as a result of vector presence comprises a sequence that is complementary to a target transcript and wherein the siRNA or shRNA is at least 15 nucleotides in length.

Still further, the methods and to recite methods of inhibiting or treating a respiratory disorder or a condition associated with expression of a respiratory virus. Support for the amendments is found in the original specification and claims as filed, and throughout the specification of co-pending application U.S.S.N. 10/ 674,159 (U.S. Pub. No. 20040242518), which was filed on the same day as the instant application and incorporated by reference therein (see paragraph 67 of the instant application for incorporation by reference). See, e.g. paragraphs 7, 8, and 132 of U.S.S.N. 10/ 674,159 for support for the amendments. .

For any or all of these reasons, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Enablement

The Examiner rejects claims 38-42, 49, 81-90, 98 and 99 under § 112, first paragraph for lacking of enabling disclosure commensurate with the scope of the claims. The Examiner at page 10 concedes that Applicant's specification enables methods of inhibiting in vivo, in a mammal, influenza target transcripts comprising administering, by intravenous injection compositions comprising a cationic

polymer complexed to siRNA specific to target transcripts. Examiner argues that the specification is nonenabling for methods of inhibiting or treating any target in any organism. Examiner alleges the specification provides no definition of "prevention." Examiner cites several references to provide support for the allegation that siRNA cannot be used as a therapeutic.

The enablement requirement relates to how the specification must be sufficient "to describe how to make and how to use the invention ... . Detailed procedures for making and using the invention may not be necessary if the description of the invention is sufficient to permit those skilled in the art how to make and use the invention" (MPEP 2164). "The standard was stated by the Supreme Court: "is the experimentation needed to practice the invention undue or unreasonable?" (MPEP 2164.1 citing *Mineral Separation v. Hyde* 242 US 261 (1916)). "The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue" (MPEP 2164.1 citing *In re Angstadt* 190 USPQ 214 (CCPA 1976)). "Compliance with the enablement requirement of 35 USC 112, first paragraph does not turn on whether an example is disclosed ... if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without undue amount of experimentation" (MPEP 2164.02, citing *In re Borkowski* 164 USPQ 642 (CCPA 1970)).

That particular applications contained within the scope of Applicant's invention may require some optimization or experimentation does not evidence that any required experimentation is undue. Examiner's statements do not show that undue experimentation is required to practice the claimed invention beyond the scope of the embodiments whose enablement was conceded by the Examiner. Examiner cites to several "post-filing" publications. These cannot erase Applicant's successful delivery of a RNAi therapeutic to a mammalian cell *in vivo*. These references identify several problems existing at or around the time of Applicant's invention, including transience of siRNA, toxicity, and inefficient delivery systems. These references nowhere cite Applicant's work described in the instant patent application. These references, rather than detract from the scope of Applicant's invention, are proof of the importance and scope of Applicant's discovery, which confronted and resolved the problems these authors identify. Applicant's teaching provides the means of making and using RNAi compositions for delivery to inhibit or prevent a disease.

Many subsequent experimental findings are evidence that Applicant's disclosure adequately teaches the skilled person how to make and use the invention without undue experimentation. In one example, PEI is used to delivery siRNA to cancer cells. The abstract of Aigner (copy attached) "Gene silencing through RNA interference (RNAi) in vivo: Strategies based on the direct application of siRNAs" J Biotechnol. 2006 Jan 10; states (emphasis added):

> RNA interference (RNAi) offers great potential not only for in vitro target validation, but also as a novel therapeutic strategy based on the highly specific and efficient silencing of

a target gene, e.g. in tumor therapy. Since it relies on small interfering RNAs (siRNAs), which are the mediators of RNAi-induced specific mRNA degradation, a major issue is the delivery of therapeutically active siRNAs into the target tissue/target cells in vivo. For safety reasons, strategies based on (viral) vector delivery may be of only limited clinical use. The more desirable approach is to directly apply catalytically active siRNAs. This review highlights the recent knowledge on the guidelines for the selection of siRNAs which show high activity in the absence of non-specific siRNA effects. It then focuses on approaches to directly use siRNA molecules in vivo and gives a comprehensive overview of in vivo studies based on the direct application of siRNAs to induce RNAi. *One promising approach is the in vivo siRNA delivery through complexation of chemically unmodified siRNAs with polyethylenimine (PEI). The anti-tumoral effects of PEI/siRNA-based targeting of tumor-relevant genes in vivo are described.*

Further Schiffelers, et al. "Cancer siRNA therapy by tumor selective delivery with ligand-targeted sterically stabilized nanoparticle" Nucleic Acids Research 2004 32(19):e149; describe similar results using PEI (emphasis added, a complete copy is attached):

> Potent sequence selective gene inhibition by siRNA 'targeted' therapeutics promises the ultimate level of specificity, but siRNA therapeutics is hindered by poor intracellular uptake, limited blood stability and non-specific immune stimulation. To address these problems, ligand-targeted, sterically stabilized nanoparticles have been adapted for siRNA. Self-assembling nanoparticles with siRNA were constructed with polyethyleneimine (PEI) that is PEGylated with an Arg-Gly-Asp (RGD) peptide ligand attached at the distal end of the polyethylene glycol (PEG), as a means to target tumor neovasculature expressing integrins and used to deliver siRNA inhibiting vascular endothelial growth factor receptor-2 (VEGF R2) expression and thereby tumor angiogenesis. *Cell delivery and activity of PEGylated PEI was found to be siRNA sequence specific and depend on the presence of peptide ligand and could be competed by free peptide. Intravenous administration into tumor-bearing mice gave selective tumor uptake, siRNA sequence-specific inhibition of protein expression within the tumor and inhibition of both tumor angiogenesis and growth rate.* The results suggest achievement of two levels of targeting: tumor tissue selective delivery via the nanoparticle ligand and gene pathway selectivity via the siRNA oligonucleotide. This opens the door for better targeted therapeutics with both tissue and gene selectivity, also to improve targeted therapies with less than ideal therapeutic targets.

Note that the latter abstract describes use of siRNA molecules targeted to specific cells, thus supporting the enablement of embodiments of Applicant's invention that recite administering a delivery enhancing moiety to enhance delivery of siRNA to a cell of interest.

Still further, the Examiner objects to use of the term "prevent" as meaning strictly "to keep from happening." Applicant respectfully points out the aforementioned dictionary definition is but one of many definitions. Applicant submits the term "prevent" in the context of medicine is not so strict as an outright elimination from occurring, but rather includes keeping back, depriving of success, and methods to avoid or avert. For example, the definition of ***prevent*** in Webster's Dictionary:

1 *archaic* **a** : to be in readiness for (as an occasion) **b** : to meet or satisfy in advance **c** : to act ahead of **d** : to go or arrive before

2 : to deprive of power or hope of acting or succeeding

3 : to keep from happening or existing <steps to *prevent* war>

4 : to hold or keep back : **HINDER, STOP** -- often used with *from intransitive senses* : to interpose an obstacle

- pre·vent·abil·i·ty /-"ven-t&-'bi-l&-tE/ *noun;* **- pre·vent·able** *also* **pre·vent·ible** /-'ven-t&-b&l/

See, www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=prevent

Further, "preventive medicine" as defined by MedTerms Medical Dictionary:

Definition of Preventive medicine: Medicine designed to avert and avoid disease. Screening for hypertension and treating it before it causes disease is good preventive medicine. Preventive medicine is a proactive approach. See, e.g., www.medterms.com.

Still further, the definition of preventive according to Dorland's Medical Dictionary:

preventive (pre·ven·tive) (pre-ven'tiv) serving to avert the occurrence of.

See, www.mercksource.com/pp/us/cns/cns_hl_dorlands.

Thus, applicant submits the Examiner has overstated that "prevention" would necessarily mean any disease or condition which was intended to be prevented would keep from happening, whether now, or anytime in the future.

Applicant maintains for any and all of these reasons that its disclosure provides sufficient enablement to comply with the statutory requirements. However, to expedite prosecution, Applicant amends claims 38,49, 81, and 84, without disclaimer of inventive subject matter, which Applicant may elect to pursue in a continuation application. Applicant amends these claims without waiver or prejudice.

For any or all of the above reasons, Applicant respectfully requests the Examiner to withdraw the outstanding rejection of the claims for failure to satisfy the enablement requirement.

Obviousness

The Examiner has rejected claims 49, 81, 83-84, 87-90 and 97-98 under § 103(a) as obvious over McCaffrrey, Aigner and Ahn.

To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest **each and every limitation** of the claimed subject matter. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See also MPEP §706.02(j), Contents of a 35 U.S.C. §103 Rejection. Applicant respectfully submits that a *prima facie* case of obviousness has not been established with respect to claim 49, 81 or claims 83-84, 87-90 depending therefrom, either as existing prior to the instant amendment or in present form.

The Examiner contends McCaffrey teaches an in vivo method of inhibiting hepatitis C in murine liver by hydrodynamic delivery of siRNA to the vascular system. Applicant respectfully submits the Examiner has overstated the teaching of this reference. McCaffrey rather utilizes a system in which plasmid DNA is hydrodynamically delivered with siRNA to obtain suppression of protein expression from the plasmid. McCaffrey does not teach or suggest a method of inhibiting a respiratory disorder or a method of treating or preventing a respiratory disease or clinical condition associated with a respiratory virus infection, necessary elements of the claims as currently amended.

The deficiencies of McCaffrey are not remedied by the teachings of Aigner or Ahn, whether alone or in combination. The Examiner contends that Aigner teaches an in vivo method of using ribozymes to inhibit expression of PTN in human tumor xenotransplants grafted in mice. The Examiner cites Aigner's supposition that PEI can be modified for use to complex between any RNA and an antibody or antibody fragment, to thereby stabilize the RNA. In contrast, Aigner fails to disclose any use of PEI to form any complex that can be used to deliver an RNAi-inducing entity, including siRNA, shRNA and/or an RNAi-inducing vector whose presence within a cell results in production of an siRNA or shRNA to cells of an organism *in vivo*. Additionally, Aigner fails to teach or suggest a method of inhibiting a respiratory disorder or a method of treating or preventing a respiratory disease or clinical condition associated with a respiratory virus infection, as recited in the claims as currently amended.

The Examiner alleges that Ahn teaches that non-viral delivery systems such as cationic polymers or other synthetic gene carriers are being investigated for delivery of DNA plasmids to circumvent the problems of using viral vectors. Applicant respectfully points out Ahn does not even mention delivery of RNA, let alone small RNAi-inducing entities molecules such as siRNA, shRNA, or vectors as recited in the instant claims. Still further, Ahn's disclosure demonstrates only in vitro transfections of DNA plasmids into cells. There is no demonstration of in vivo delivery of any nucleic acid, much less teaching of any methods of treating preventing or inhibiting a respiratory disorder. Ahn's disclosure accordingly

constitutes a generalized description of known experimental systems for in vitro delivery of large, circular DNA molecules and goes no further than that.

Thus, for any or all of the reasons discussed above, Applicant submits a *prima facie* case of obviousness has not been made. Applicant respectfully requests the Examiner to withdraw the obviousness rejection of the claims.

In summary, Applicant respectfully submits that the present case is in condition for allowance. In advance of such action, rejoinder of the additional species and claims reading thereon is respectfully requested. Should the Examiner maintain that some of the issues addressed herein remain unresolved, the undersigned would appreciate the opportunity to discuss such issues at the Examiner's convenience and hereby requests an Examiner interview by telephone for this purpose.

A petition for a three (3) month extension of time and American Express credit card form to cover the fee for an extension of time are enclosed. It is believed no additional fees are due in association with filing of these papers, however, in the event any additional fees are due, please charge any additional fees associated with this filing, or apply any credits, to our Deposit Account No. 03-1721.

Respectfully submitted,

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ANMERKUNG ZUR ENTSCHEIDUNG ÜBER DIE ERTEILUNG EINES EUROPÄISCHEN PATENTS (EPA Form 2006)

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1. **EPO Information Brochure "National law relating to the EPC".**
   This brochure provides useful information regarding formal requirements and the steps to be taken before the patent authorities of the Contracting States in order to acquire rights in those states. Since the necessary steps are subject to change the latest edition of the brochure should always be used. Subsequent information is published in the Official Journal.

2. **Translation of the European patent specification under Article 65(1) of the European Patent Convention**
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